Office of Device Evaluation

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Subject: BLA 98-0012
cA2 (Infliximab) Avakine™ Lyophilized Concentrate for Infusion
Centocor, Inc.

Date: April 24, 1998

BLA 98-0012

This evaluation is written for the review of the new application number BLA 98-0012, Chimeric (Human-Murine) Monoclonal Antibody (cA2) to Tumor Necrosis Factor for Inflammatory Bowel Disease, Therapeutic Agent for Crohn's Disease, (Infliximab) Avakine™ Lyophilized Concentrate for Infusion, by Centocor, Inc. The sponsor stated that "Infliximab is indicated for the treatment of patients with Crohn's disease to: reduce signs and symptoms in patients with moderated to severe disease activity in whom conventional therapies are inadequate, [and to] close enterocutaneous fistula" (sponsor's submission, Vol. 1, p. 8).

Dr. Barbara Matthews, the lead clinical reviewer on the BLA 98-0012 review team, had requested this gastroenterological review of the endoscopic and peri-rectal data presented by the sponsor relating to the efficacy of the cA2 on the clinical course of Crohn's disease.

Background

Crohn's disease is a complex spectrum of clinical and pathologic features typified by focal asymmetric transmural and granulomatous inflammation of the gastrointestinal tract. The treatments for Crohn's disease are as varied as its clinical manifestations. An attempt has been made by the American College of Gastroenterology (ACG) Practice Parameters Committee, to provide guidance on the treatment of the various aspects of Crohn's disease. These "Guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems, as established by interpretation and collation of scientifically valid research, derived from extensive review of published literature. When data are not available that will withstand objective scrutiny, a recommendation may be made based on a consensus of experts" (Hanauer, S.B., Meyers, S., "Management of Crohn's Disease in Adults" (1997), Am. J. Gastro., 92(4): 559-566). A copy of this journal article has been included with this memo, and provide a accurate overview of the current clinical practice in the treatment of Crohn's disease.

Clinical Data & Analysis

The sponsor has provided the following definitions for terms used in the efficacy measurement of cA2:

> "CDAI = Crohn's Disease Activity Index-a composite disease activity index comprising assessments of diarrhea, abdominal pain, general well-being, abdominal masses, extraintestinal manifestations of disease and changes in hematocrit and body weight. A CDAI < 150 is regarded as being in remission, while ≥ 150 is regarded as active disease...
> IBDQ = Inflammatory Bowel Disease Questionnaire (a quality-of-life instrument with scores that range from 32 to 224). Higher scores indicate better quality of life: score ≥ 170 are associated with clinical remission.
> CDEIS = Crohn's Disease Endoscopic Index of Severity. The CDEIS evaluates the presence of mucosal lesions and the intestinal surface affected by disease for 5 segments of the intestine: rectum, sigmoid and left colon, transverse colon, right colon and ileum. Lower scores indicate endoscopic improvement" (sponsor's submission, Vol. 1, p. 6).

The sponsor has outlined the clinical trials for the use of cA2 in the treatment of Crohn's disease as follows:

C0168**T08**: Phase I open-label study in 10 patients (all received cA2),

C0168**T11**: Phase II, open-label, sequential-dose study in 21 patients (all received cA2),

C0168**T16**: Phase II/III, placebo-controlled, double-blind, randomized, dose-ranging study followed by an open-label extension

C0168**T20**: Phase III, placebo-controlled, double-blind, randomized, dose-ranging study in 94 patients with fistulizing Crohn's disease (63 patients received cA2 and 31 patients received placebo). (sponsor's submission, Vol. 1, p. 80).

During this premarket evaluation process, I have reviewed all the endoscopy video tapes and the computer based enterocutaneous fistula images provided by the sponsor, in collaboration with the lead clinical reviewer, Barbara Matthews, M.D. (CBER).

Tape 1 (T8)/Patient —

May 12, 1993. Poor bowel preparation of cecum. Mild disease right colon, with increasing erythema, edema and ulceration, transverse to left colon. Superficial ulceration proximal left colon to rectum.

June 14, 1993. Improved bowel preparation over previous endoscopy. No significant disease in cecum or right colon. Improvement in erythema, edema and ulceration, in the transverse to left colon observed since last endoscopy.

July 9, 1993. Increased erythema, edema and ulceration, in transverse to left colon since endoscopy four weeks previous.

Tape 1 (T8)/Patient —

September 1, 1993. Cecum visualized. Presence of pseudo-polyps, moderate inflammatory exudates, edema throughout colon, with loss of architecture in transverse colon.

September 30, 1993. Improved erythema/edema, with decreased number of pseudo-polyps. Greatest improvement in left colon. Continued loss of architecture in transverse colon.

October 27, 1993. Continued improved erythema/edema, with decreased number of pseudo-polyps. Left colon appears normal with good vascular pattern. However, continued loss of architecture is observed in transverse colon.

Tape 2 (T8)/Patient —

September 22, 1993. The cecum revealed moderate edema and erythema, with scattered ulceration. The right colon was minimally involved, with a return of erythema and significant edema in the mid-transverse colon resulting in the loss of normal architecture in this region. Moderate inflammatory exudates and skip lesions were also noted from this mid-transverse region to the left colon, where asymmetric erythema/edema with clusters of pseudo-polyps were observed. Mild ulceration was noted in the sigmoid, with the presence of normal appearing mucosa in the rectum.

October 20, 1993. The terminal ileum appeared to be normal. Decreased edema and erythema were observed in the right colon. The severity of the disease in the mid-transverse colon had decreased, with a shorter length of mucosal involvement observed. The left colon was observed to have less edema.

November 11, 1993. The terminal ileum continued to appear normal. In general, each portion of the colon had continued decrease in edema and erythema.

Tape 2 (T8)/Patient —

September 27, 1993. The terminal ileum appeared to be normal., whereas there is mild edema in the cecum. This edema increased in the transverse, left, and sigmoid colon. The left sided colonic lesions included aphthous ulcerations, changes in mucosal vasculature, and mild inflammatory exudates.

October 20, 1993. In general, there is minimal erythema and edema from the cecum to the sigmoid colon. There was been complete resolution of the aphthous ulcerations and inflammatory exudates.

November 26, 1993. Poor bowel preparation. Unable to adequately visualize the colon.

Tape 3 (T8)/Patient —

September 9, 1993 (October 13, 1993 in Vol. 39, p. 280). Entire colon revealed severe edema, and erythema (pan-colitis). There were scattered bleeding lesions, cobblestone formations, inflammatory exudates. The disease appeared to be less severe in the left colon and in the cecum.

November 10, 1993. Significant improvement in right sided edema, and erythema. Partial healing of scattered bleeding lesions, cobblestone formations, inflammatory exudates. Mild rectal disease present.

Tape 3 (T8)/Patient —

February 23, 1994 (March 1, 1994 in Vol. 39, p. 284). Moderate erythema and edema throughout entire colon, with multiple/diffuse pseudo-polyps, aphthous ulcerations and inflammatory exudates.

"4 weeks" (April 6, 1994 in Vol. 39, p. 285). Significant healing of pseudo-polyps, aphthous ulcerations and inflammatory exudates throughout colon, with decreased erythema and edema.

"8 weeks" (December 23, 1994 in Vol. 39, p. 286). Normal mucosa in entire colon.

Tape 3 (T8)/Patient —

No recorded images presented.

Tape 3 (T8)/Patient —

March 7, 1993. Severe right-sided erythema and edema, with pseudo-polyps, inflammatory exudates, and cobblestone formations. The left colon contained moderate edema and mucosal friability.

April 12, 1994. Significant healing of right-sided pseudo-polyps, inflammatory exudates, and cobblestone formations. Decreased erythema and edema were observed throughout the colon.

May 10, 1994. Mild to minimal mucosal erythema and edema throughout the entire colon, with complete healing of mucosal lesions.

Tape 4 (T8)/Patient —

April 5, 1994. It appeared that patient had a history of colonic surgery with primary re-anastomosis. What appeared to be the remaining right colon revealed moderated erythema and edema, with scattered inflammatory exudates into the transverse colon. There was minimal erythema observed in the left colon.

May 9, 1994. Persistent ulceration and inflammatory exudates observed, with ulceration at the site of previous surgical anastomosis.

Tape 4 (T8)/Patient —

May 4, 1994. Severe mucosal disease from cecum to left colon with multiple skip lesions. Severe erythema, edema right colon, with pseudo-polyps and cobblestone formations. The left colon revealed multiple areas of cobblestone formations.

June 7, 1994. Poor bowel preparation, but able to observe some decrease in cobblestone formations and mucosal healing.

July 1, 1994. Poor bowel preparation, but able to observe further decrease in cobblestone formations and possible complete mucosal healing.

Analysis:

In general, there is agreement with the investigator's description of the endoscopy videos and what was observed by the FDA clinical review team. There were some differences in the dates assigned to certain videos, but these differences were explained by the sponsor in Volume 39 of the submission.

However, in those patients where significant resolution of mucosal lesions were noted in the investigator's narrative, the endoscopy videos provided by the sponsor, supported these conclusions.

Male & Female Enterocutaneous Fistulae Diagrams:

I have reviewed the computer images of the enterocutaneous fistulae diagrams from the T20 study with lead clinical reviewer, Barbara Matthews, M.D. In general, there is a concern that since the clinical end-point was not complete healing of the fistulae, but the lack of drainage from these fistulae (with gentle pressure), it would be difficult to determine cA2 success in borderline cases just by looking at the computer images. In addition, determining the difference between draining and non-draining (but non-healed) peri-vaginal fistulae, would be difficult both in person and by computer image.

Analysis:

In general, there was agreement between the investigator's interpretation of which fistulae had healed and the determination by the FDA clinical review team.

Conclusions:

These specific differences in end-point interpretations have been used by lead clinical reviewer, Barbara Matthews, M.D., to re-analyze the sponsor's T20 clinical trial data and have been outlined in her clinical review memo.

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